

IN THE SPECIFICATION:

Please amend as follows. Text added to the paragraph is presented in bolded underlined format, while text to be deleted is presented in bolded strike-through format.

Please replace paragraph [0066] with the following paragraph:

[0066] The cDNA for human cytochrome CYP2D6 has been cloned and sequenced (Gonzalez et al., 1988). The genomic sequence of CYP2D6 is also known. CYP2D6 encompasses 9 exons spanning 4.66 kb at chromosomal locus 22q13.1. These and other CYP2D6 sequences are available from databases such as ~~GenBank~~ **GENBANK** (Accession numbers XM_040063, XM_040066, XM_040064, XM_040062, XM_040060, XM_013013, and XM_040065). The availability of these sequences and the advent of molecular genetics has made possible pharmacogenetic studies of CYP2D6.

Please replace paragraph [0100] with the following paragraph:

[0100] Examples of apparatuses that may be useful for electrophoresis and visualization are an agarose gel electrophoresis apparatus, such as CBS Scientific horizontal mini-gel; a power supply having a constant voltage of 200V or better variable power supply for electrophoresis, such as the BioRad Model 200; photodocumentation apparatus, such as the Alpha Innotech ~~AlphaImager~~ **ALPHAIMAGER** or Polaroid DS34 t; and a transilluminator, e.g., a VWR Model LM-20E or equivalent.

Please replace paragraph [0102] with the following paragraph:

[0102] Centrifugation is carried ~~out~~ in ~~a BioMek~~ **BIOMEK** 2000 or Vortex (VWR; G-560) instruments and centrifuges for spinning PCR trays (~~Sorvall~~ **SORVALL** T6000D).). The 96-well-plate centrifugation system from ~~Qiagen~~ **QIAGEN** may also be used. Microcentrifuges such as those from Eppendorf are used with Microcentrifuge tubes (from, e.g., National Scientific, CN065S-GT).

Please replace paragraph [0104] with the following paragraph:

[0104] For DNA amplification (PCR), 2 ml MicroTubes with screw caps (Sarstedt; 72.693-005) may be used. A variety of 96-well plates suitable for PCR and other manipulations can be used. In the Examples herein, ABI ~~MicroAmp~~ **MICROAMP** Optical 96-well Reaction Plates (P/N#N801-0560) are used with ABI 96-well Plate Septa (P/N#4315933), or Microseal 96-well PCR microplates (MJ Research, MSP-9601) are used with Microseal A sealing film for microplates (MJ Research, MSA-5001). A 96-place storage system exemplified by VWR #30128-330, is used to store plates containing samples between steps in the assay.

Please replace paragraph [0106] with the following paragraph:

[0106] A PCR cycler capable of processing 96-well plates is used in the Examples. Exemplary PCT thermal cyclers include the ~~GeneAmp~~ **GENEAMP** 9600 (Perkin-Elmer) or the PTC 200 (MJ Research). The MJR PTC 200 has features that are desirable regardless of which instrument is used: heating rates of up to 3°C/second, which reduce reaction times, and rapid temperature homogeneity (e.g., $\pm 0.4^{\circ}\text{C}$ within 30 seconds at 90°C). The heating block that is used may be, for example, VWR's Heat Block (VWR, 13259-007).

Please replace paragraph [0108] with the following paragraph:

[0108] In order to process a large number of samples for CYP2D6 genotyping, a multipurpose automated or semi-automated programmable workstation is used (Meldrum, Automation for Genomics, Part One: Preparation for Sequencing, Genome Research, 10:1081-1092, 2000; Meldrum, Automation for Genomics, Part Two: Sequencers, Microarrays, and Future Trends, Genome Research, 10:1288-1303, 2000). Preferred features of the workstation include the ability to rapidly and accurately pipette, dilute and dispense small volumes of liquids. The exemplary ~~programable~~ **programmable** workstation used herein is the ~~BioMek~~® **BIOMEK** 2000 (Beckman Coulter, Inc.).

Please replace paragraph [0114] with the following paragraph:

[0114] 3.1.1 Agarose, ~~SeaKem~~ **SEAKEM** GTG (FMC 50074). Store ambient (18°C-26°C), stable for 1 year.

Please replace paragraph [0142] with the following paragraph:

[0142] 3.3.2 HotStarTaq™ PCR Core Kit (~~Qiagen~~ **QIAGEN** 203203 or 203205) (HotStarTaq™ enzyme, 25mMg++, M10X buffer & 5X Q Solution), stable for 1 year when stored at -10°C to -30°C.

Please replace paragraph [0150] with the following paragraph:

[0150] 3.5.2 ABI ~~GeneScan~~ **GENESCAN**-120 LIZ Size Standard (P/N4322362), stable for six months when stored at 2 to 10°C.

Please replace paragraph [0158] with the following paragraph:

[0158] 3.8.1.2 Long PCR CYP2D6 and CYP2D6D Duplex Mix is prepared according to the following recipe.

Components	For 114 Rxns
10X Qiagen <u>QIAGEN</u> PCR Buffer	285.0 µL
5X Q Solution	570.0 µL
25 mM dNTP mix	28.5 µL
5X primer mix (2D6&2D6D) [3.8.1.1, above]	570.0 µL
H2O	1100.1 µL
Total	2553.6 µL

Please replace paragraph [0162] with the following paragraph:

[0162] 3.8.2.2 Long PCR: CYP2D6 and CYP2D6x2 PCR Mix is prepared according to the following recipe.

Components	for 114 Rxns
10X Qiagen <u>QIAGEN</u> PCR Buffer	285.0 μ L
5X Q Solution	570.0 μ L
25 mM dNTP mix	28.5 μ L
5X primer mix (2D6 and 2D6x2) [3.8.2.1, above]	570.0 μ L
H ₂ O	1100.1 μ L
Total	2553.6 μL

Please replace paragraph [0171] with the following paragraph:

[0171] Five (5) μ l of ABI SNaPshot Ready Mix, 1 μ l of Primer Extension Primer Mix and 1 μ l Sterile H₂O are combined to a final volume of 7 μ l per reaction. The Mix is prepared fresh before each use, and kept on ice until used.

Reagent	Per Well	Per Plate*
SnaPshot <u>SNaPshot</u> Ready Mix	5 μ l	560 μ l
Extension Primer Mix	1 μ l	112 μ l
DH ₂ O	1 μ l	112 μ l

Total	7 µl	784 µl
--------------	-------------	---------------

*Contains extra for aliquot by **BioMek BIOMEK** 2000.

Please replace paragraph [0173] with the following paragraph:

[0173] For each reaction, 1 µl of SAP (1 unit/µl) and 1 µl of water are combined to a final volume of 2 µl. The SAP cocktail is freshly prepared before each use.

Reagent	Per Well	Per Plate*
SAP	1 µl	140 µl
Dh2O	1 µl	140 µl
Total	2 µl	280 µl

*Contains extra for aliquot by **BioMek BIOMEK** 2000.

Please replace paragraph [0174] with the following paragraph:

[0174] 3.8.8 Loading Mix: Ten (10) µl of Hi-Di Formamide and 0.5 µl **GeneScan GENESCAN** 120 LIZ Size Standard are combined to a final volume of 10.5 µl per sample. Lodging Mix is prepared fresh before each use.

Reagent	Per Well	Per Plate*
Hi-Di Formamide	10 µl	1120 µl
GeneScan <u>GENESCAN</u> 120 LIZ Size Standard	0.5 µl	56 µl
Total	10.5 µl	1176 µl

*This setup is for a full 96 well plate.

Please replace paragraph [0178] with the following paragraph:

[0178] PCR master mix (CYP2D6 and CYP2D6D Duplex Mix) is prepared according to Example 3.8.1.2 and is used in the reaction. The following table describes a recipe that results in a sufficient volume for a full PCR plate (sample tray; 96-wells), and allows for excessive solution to enable pipetting from a trough with an 8-channel pipettor into all PCR wells.

	1 Rxn	Cocktail x 56 (1/2 plate)	Cocktail x 112 (full plate)
Master Mix [3.8.1.2]	22.4 μ L	1254.4 μ L	2508.8 μ L
HotStarTaq	0.3 μ L	16.8 μ L	33.6 μ L
Taq Extender	0.3 μ L	16.8 μ L	33.6 μ L
Qiagen <u>QIAGEN</u> DNA*	2.0 μ L	----	----
Total	25 μL		

Please replace paragraph [0181] with the following paragraph:

[0181] PCR master mix (CYP2D6x2 PCR Mix) is prepared according to Example 3.8.2.2 and is used in the reaction. The following table describes a recipe that results in a sufficient volume for a full PCR plate (sample tray), and allows for excessive solution to enable pipetting from a trough with an 8-channel pipettor into all PCR wells.

	1 Rxn	Cocktail x 56 (1/2 plate)	Cocktail x 112 (full plate)
Master Mix [3.8.2.2]	22.4 μ L	1254.4 μ L	2508.8 μ L units
HotStarTaq	0.3 μ L	16.8 μ L	33.6 μ L
Taq Extender	0.3 μ L	16.8 μ L	33.6 μ L
Qiagen <u>QIAGEN</u> DNA*	2.0 μ L	----	----
Total	25 μL		

Please replace paragraph [0184] with the following paragraph:

[0184] For automated PCR setup on the **BioMek BIOMEK** 2000 robotic workstation, the PCR tray, a box of Robbins 125 µL pipet tips, a box of 20 µL pipet tips, the **Qiagen QIAGEN** sample tray and the reagent reservoir (trough) are placed at the appropriate positions on the **BioMek BIOMEK** work surface. If the PCR or subsequent steps are set up manually, the same master mix recipe/digestion recipe is used, and the assay proceeds as described below without the **BioMek BIOMEK**, and single or multichannel pipettors and tips are used.

Please replace paragraph [0185] with the following paragraph:

[0185] The master mix is added to the reagent reservoir. Eight positions at the end of the **Qiagen QIAGEN** sample tray are left open for controls. The sample tray is briefly spun down in a plate centrifuge outside of the master mix and template addition area (i.e., in a clean room). The control samples (typically, four positive and two negative controls) are placed in the appropriate positions in the sample tray.

Please replace paragraph [0186] with the following paragraph:

[0186] The **BioMek BIOMEK** station first pipets 23 µl of the master mix into each 0.2 ml PCR tray wells, and then adds 2 µl specimen DNA or control. The wells are tightly sealed with PCR tube caps or Microseal A film. The sample tray is briefly (~ 5 s) vortexed and spun down for about 30 s in a plate centrifuge at 2,000-6,000g (1,600 rpm in a **Sorvall SORVALL** T6000D centrifuge).

Please replace paragraph [0202] with the following paragraph:

[0202] SAP-digested samples are prepared according to Example 4.5 for loading using a **BioMek BIOMEK** 2000. The SNaPSHOT product is diluted 15-fold with water, and then 2 µl of the diluted product is mixed with 10.5 µl of the Loading Mix. The plate is covered with septa, vortexed and spun down in the plate centrifuge. The plate is heated at 95°C for 5 minutes, then

immediately placed on ice for 3 minutes or until use. The plate is spun down in a plate centrifuge to collect condensation. The plate is then assembled and loaded onto the ABI3100 Genetic Analyzer.